- UPDATE -
Implementation and roll-out of Xpert MTB/RIF
May 2013

This document provides an update on the global roll-out of the Xpert MTB/RIF assay, recommended by WHO for the rapid and simultaneous detection of TB and rifampicin resistance. For background and guidance on use of the test, including the WHO Policy Statement, Rapid Implementation document and Checklist of prerequisites to country implementation, as well as published literature, visit http://www.who.int/tb/laboratory/mtbrifrollout.

Outcomes of the Global Forum of Xpert MTB/RIF implementers – Annecy, France, 16-17 April 2013

Implementers of Xpert MTB/RIF gathered with technical partners and donors to discuss experiences, challenges and evidence of impact in rolling-out the technology, as part of the 5th Global Laboratory Initiative (GLI) Partners meeting in Annecy, France. Meeting presentations can be accessed via the online agenda: Agenda with links to presentations

Findings and recurring points discussed at the meeting included:

- **Evidence of impact:** High-burden countries including South Africa, Brazil, India, Moldova, Viet Nam and the Philippines, and multi-national initiatives including TB CARE I, TB REACH and MSF highlighted the impact found in piloting or in wide-scale implementation of Xpert MTB/RIF. Significant increases in bacteriologically positive TB case detection were reported by several implementers, when compared to conventional diagnostic algorithms based on microscopy. Numbers of rifampicin-resistant cases were also found to increase significantly. While many implementers indicated a reduction in time to diagnosis, there was less evidence of reductions in time to initiate treatment. In some cases, this was due to weak systems that prevent the efficient delivery of Xpert MTB/RIF results to treating clinicians or otherwise impede a rapid start to treatment; in other cases, this was due to the absence of a monitoring system to collect the data needed to evaluate the time between diagnosis and treatment. Implementers repeatedly indicated the need for strong monitoring and evaluation to demonstrate impact and to guide policy uptake at country level

- **Cost and cost-effectiveness:** A review of the evidence showed that the use of Xpert MTB/RIF to diagnose TB and MDR-TB is cost-effective compared with current practices, for all individuals presumed to have TB, including those with HIV co-infection. The use of Xpert MTB/RIF is more costly compared to microscopy, but increased costs represent a small share of available TB funding. The majority of existing costing and cost-effectiveness studies are from South Africa, so there remains a need for further evidence from other countries and epidemiological settings. Using Xpert MTB/RIF has also been modeled to be cost-saving for patients, though more setting-specific data on patient costs is much needed.

- **Country scale-up plans:** Selected countries indicated ambitious plans for scaling-up use of Xpert MTB/RIF, including:
  - **South Africa:** Having already opted to switch from microscopy to Xpert MTB/RIF as the initial diagnostic test for all TB suspects, the national roll-out plan for Xpert MTB/RIF is now expanding to include mines and correctional services. The country has already performed 1.2 million tests with a 14.6% MTB positivity rate.
  - **Brazil:** Like South Africa, Brazil plans to replace microscopy with Xpert MTB/RIF as the initial diagnostic test nationwide. The country is also planning to create a sentinel surveillance system for MDR-TB and a national laboratory database incorporating Xpert MTB/RIF.
  - **China:** After positive outcomes of a validation study, China plans to buy >900 GeneXperts in 2013-2014, pending a license from the State Food and Drug Administration (China SFDA).
  - **Moldova:** Moldova's TB REACH-supported project has rapidly rolled-out 25 GeneXperts to the peripheral (district) level. The country plans to reach 100% population coverage with Xpert MTB/RIF in 2015.
  - **Philippines:** As part of a wide scale-up plan using Xpert MTB/RIF, approximately 10 GeneXperts will be specifically positioned to diagnose paediatric and extrapulmonary TB.
  - **India:** Twelve labs recently supplied with GeneXperts under the EXPAND-TB project for detection of rifampicin resistance are expected to diagnose 7,000 rifampicin-resistant cases annually.
  - **Vietnam:** Support from the Global Fund and the UNITAID-supported TBXpert project will allow the country to more than double its current capacity for using Xpert MTB/RIF.

- **Cartridge shortages:** Global shortages of Xpert MTB/RIF cartridges in recent months, resulting from manufacturing problems in scaling-up to meet increasing demand, threaten the efficient functioning of programmes and sites that have already adopted Xpert MTB/RIF into their diagnostic and clinical algorithms, and also may introduce delay to new large-scale country plans and multi-national initiatives. Cepheid has indicated that the problem is expected to be fully resolved by the end of Q3 2013 and has issued a communiqué. Donors and major implementers expressed a need for improved forecasting to aid Cepheid in planning to meet demand.
- **Electronic recording and reporting:** A panel of partners together with Cepheid discussed progress in development and plans for electronic recording and reporting systems. Interactive Research and Development (IRD) and Abt Associates shared their innovations in automated reporting of results, including the use of SMS alerts that allow patients to be more quickly started on treatment. A remote monitoring tool with centralized data control by the customer is expected to be launched by Cepheid by the end of 2013.
- **Calibration:** As the first adopters of Xpert MTB/RIF have now been using their machines for over a year, annual calibration was raised by a number of implementers, including the need to plan and budget accordingly. Remote calibration is expected to significantly reduce the need to swap modules, though still entails special planning and requires the ability of users to save and send electronic files.
- **Matching diagnostic and treatment capacity for drug-resistant TB:** As significant increases in rifampicin-resistant TB cases were frequently found after introducing Xpert MTB/RIF, country reports once again highlighted the urgent need to scale-up treatment capacity. Planning for increased treatment capacity in parallel with diagnostic capacity allows for countries to maximize the benefit of implementing Xpert MTB/RIF.
- **Recording and reporting:** The introduction of Xpert MTB/RIF has required countries to revise their forms and registers accordingly. The revised WHO Definitions and Reporting Framework was presented and discussed. (see more information below under “New publications”)
- **Engaging the private sector:** Within the framework of the TBXpert Project and with TB REACH support, Interactive Research and Development (IRD) is establishing novel public-private partnerships in cooperation with local partners and NTPs in Bangladesh, Indonesia and Pakistan. The social business models will accelerate uptake and increase demand from patients seeking care in the private sector, providing free Xpert MTB/RIF testing and free treatment for all TB cases detected, while ensuring sustainability by generating revenue through adjunct tests and services.
- **Quality assurance:** A need exists to develop a quality assurance model for Xpert MTB/RIF, which incorporates both initial verification of module functioning as well as proficiency testing of users. A taskforce of partners led by PATH has been formed to establish a recommended model, which would be linked with existing national TB external quality assurance programmes.
- **Diagnostic and clinical algorithms:** Implementers shared their country-specific diagnostic and clinical algorithms incorporating Xpert MTB/RIF with other TB diagnostics, and emphasized the need to allocate sufficient resources for training doctors and nurses to ensure rapid and appropriate treatment of patients detected. Continuous monitoring of performance allows for review and optimization of algorithms.
- **Errors and invalid results:** Errors and invalid results were generally found to decline over time with adequate training and troubleshooting. Evidence was presented showing a reduction in false rifampicin resistant results using the new G4 version Xpert MTB/RIF cartridge.
- **Research and development:** While Xpert MTB/RIF has significant advantages over conventional tests, it is not a perfect point-of-care test. The need for fast followers was raised, and Treatment Action Group (TAG) made a strong case for the need to increase funding for research in new diagnostics as total R&D investments in TB have grown only modestly in recent years.
- **Partner collaboration and coordination**: In-country partner coordination must be led by NTPs and is critical to ensure the most efficient use of resources and a unified strategy, prevent site stock-outs and expiry of cartridges, facilitate sustainability, enable the sharing of best practices and align M&E frameworks. Xpert MTB/RIF should be integrated into national TB laboratory strategies and programme strategies.

New publications

Prompted by the need to accommodate Xpert MTB/RIF into revised case and outcome definitions, WHO has issued the **Definitions and reporting framework for tuberculosis (2013 revision)**. The document provides examples of laboratory registers, a specimen examination request form, a basic management unit TB register and a second-line TB treatment register integrating Xpert MTB/RIF, and introduces the following key changes to definitions and reporting related to Xpert MTB/RIF in particular:

- A *bacteriologically confirmed TB case* is one from whom a biological specimen is positive by smear microscopy, culture or WHO-approved rapid diagnostic (such as Xpert MTB/RIF).
- The treatment outcome "cured" is defined as a pulmonary TB patient *with bacteriologically confirmed TB* at the beginning of treatment who was smear- or culture-negative in the last month of treatment and on at least one previous occasion.
- Quarterly reports on TB case registration and treatment outcomes in the basic management unit now stratify on bacteriological confirmation instead of smear positivity.
- A new classification has been introduced: TB patients with rifampicin resistance, defined as resistance to rifampicin detected using phenotypic or genotypic methods, with or without resistance to other anti-TB drugs.
- Annual reporting of treatment outcomes aggregates TB cases with rifampicin resistance (detected for example using Xpert MTB/RIF) with TB cases with multidrug resistance (MDR-TB), if such patients are treated with a full MDR-TB regimen.

The revised definitions will be used by WHO as the basis for global data collection starting in 2014 for year 2013 data. The document introduces other changes in addition to those mentioned above, and countries may choose to customize their definitions and reporting framework as needed. The document can be downloaded here.

WHO Information Note on the use of Xpert MTB/RIF for increasing the timely detection of TB among people living with HIV. Developed jointly by the WHO Stop TB and HIV Departments, this document describes the early evidence (research and modelling results) on use of Xpert MTB/RIF in people living with HIV and presumed to have TB, and provides management algorithms

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Lawn SD et al. *Advances in tuberculosis diagnostics: the Xpert MTB/RIF assay and future prospects for a point-of-care test*. Lancet Infect Diseases 13(4). April 2013: 349–361.
http://www.sciencedirect.com/science/article/pii/S1473309913700082
The authors review the rapidly growing body of scientific literature and discuss the advantages and challenges of using Xpert MTB/RIF. The authors also review other prospects within the TB diagnostic pipeline.

A list of published references about Xpert MTB/RIF continues to be regularly updated by WHO. Articles are categorized by topic: paediatric TB, extrapulmonary TB, cost-effectiveness, etc. This resource is available at:
http://www.stoptb.org/wg/gli/assets/documents/map/XpertPublications.pdf.

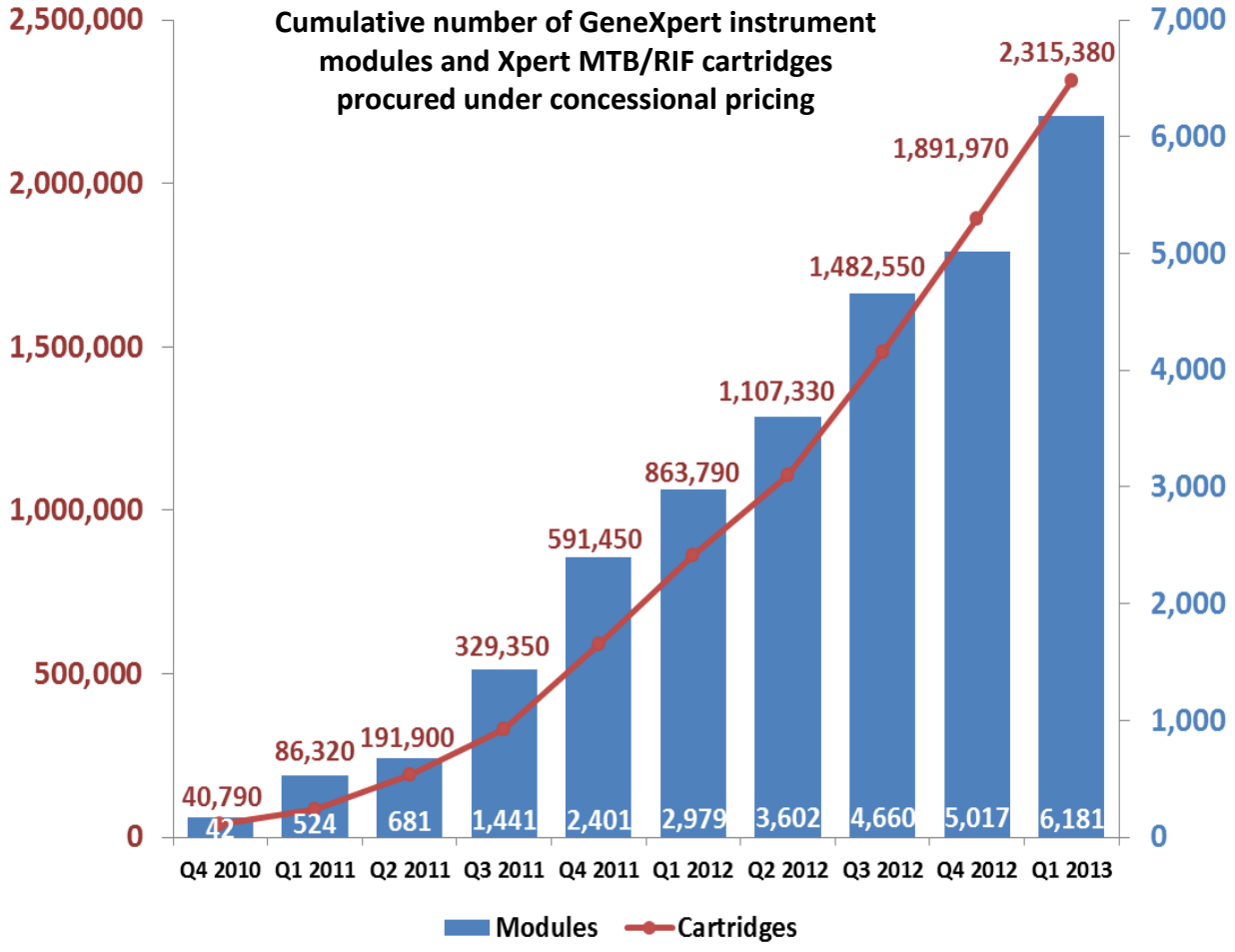
News

- WHO convened an Expert Group Meeting on 20-21 May to review existing evidence on the use of Xpert MTB/RIF for **diagnosis of pulmonary, extrapulmonary and paediatric TB**, and associated rifampicin resistance. The recommendations of the Expert Group will be presented to the WHO Strategic and Technical Advisory Group for TB (STAG-TB) for review on 11-12 June, with subsequent policy guidance issued by WHO.
- The **EXPAND-TB Project**, a multi-partner initiative to strengthen laboratory capacity for detecting drug-resistant TB and establish rapid diagnostics in 27 countries, has added Xpert MTB/RIF to its list of rapid diagnostics for implementation in selected countries. A total of 65 GeneXperts and approximately 300,000 Xpert MTB/RIF cartridges will be provided to 15 countries. Launched in 2008, the EXPAND-TB Project is a collaboration among WHO, the Global Laboratory Initiative (GLI), the Foundation for Innovative New Diagnostics (FIND) and the Stop TB Partnership Global Drug Facility (GDF), funded by UNITAID and other partners. More details on the EXPAND-TB Project can be found here.
- WHO and the Stop TB Partnership have launched the **TBXpert Project**, a 3-year USD25.9 million UNITAID-funded project to provide 1.4 million Xpert MTB/RIF test cartridges and over 220 GeneXperts in 21 recipient countries. Partners include GLI, TB REACH, GDF, the EXPAND-TB Project, Interactive Research and Development (IRD) and the African Society for Laboratory Medicine (ASLM). More details on the TBXpert Project can be found here.

Monitoring the global roll-out of Xpert MTB/RIF

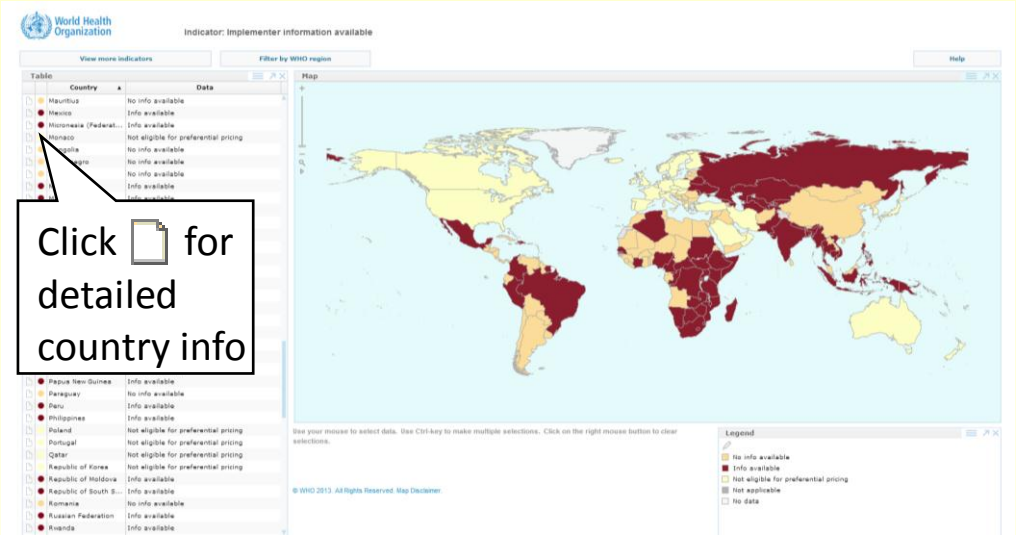
The Laboratories, Diagnostics and Drug Resistance Unit of the WHO Stop TB Department maintains a website (http://www.who.int/tb/laboratory/mtbrifrollout) monitoring the roll-out of Xpert MTB/RIF, in order to facilitate coordination among implementers, including countries, technical agencies, NGOs, and other partners.

By the end of March 2013, a total of 1,123 GeneXpert instruments (comprising 6,181 modules) and 2,315,380 Xpert MTB/RIF cartridges had been procured in the public sector in 83 of the 145 countries eligible for concessional pricing.



Countries with the largest numbers of procured cartridges under concessional pricing, as of 31 March 2013: South Africa (1,388,450), India (110,110), Kenya (64,320), Zimbabwe (51,280), Tanzania (47,850), Swaziland (39,170), Pakistan (37,550), Brazil (34,260), Nigeria (31,440), Mozambique (29,560)

WHO collects and shares information from National TB control programmes and partners describing the placement of instruments, planned orders, and funding sources. This information, including detailed information by country, is available at: http://www.stoptb.org/wg/gli/assets/documents/map/2/atlas.html



Countries for which the National TB control programme and/or partners have shared detailed information on placement of instruments, funding, and planned orders

In order to have the most comprehensive and up-to-date information to facilitate coordination, we rely on all country implementers, partners, and funders to notify us of any updates/changes. A reporting form can be found at: http://www.stoptb.org/wg/gli/assets/documents/map/2/XpertMTBRIFreportingform.doc

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